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EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	09/858,200	MAKRIGIORGOS, GERASSIMOS M.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☒ Claim(s) *12,13,17,19,20 and 25* is/are allowed.

6)☒ Claim(s) *1-11,16,18 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/31/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 11/24/04. Claims 1, 3, 4, 5, 6, 9, 10, and 16 have been amended, and claims 17-25 have been added. Claims 1-25 are pending, claims 14-15 are withdrawn from prosecution. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Priority

2. Applicant's amendment to the specification has been entered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3, 16, 18, and 21-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Any previously set forth 112 2nd rejection which is not reiterated or particularly addressed is withdrawn in view of applicant's amendments to the claims.

In claim 3, the phrase "each whole gene on the mutation scanning array" lacks proper antecedent basis in the claim as the claim does not previously require whole genes on the mutation scanning array, only that the oligonucleotides "collectively span at least 10 different array genes from the 5' to 3' end." The collective spanning could include only portions of the genes from one end to another, and thus the independent claim does no include antecedent basis for the limitation. This rejection is a modification of the previously set forth rejection in view of the amended claim. No specific arguments were provided to address this rejection which is modified from the previous office action.

Claim 16 is indefinite over the recitation "comprises at least 5 genes, each of which is contiguous" because it is not clear if this means that a the target DNA sequence contains 5 genes that are each contiguous with respect to the genes themselves (i.e. intact) or if the claim intends that the 5 genes are contiguous with one another within the genome from which the sample was taken, for example within a genomic chromosome. Applicant's remarks state that the claim was amended to make explicit that the each target gene is a contiguous gene, but this is not persuasive because it is still not clear what that means, as discussed in this paragraph.

In claim 18 the phrase "each whole gene on the mutation scanning array" lacks proper antecedent basis in the claim as the claim does not previously require whole genes on the mutation scanning array, only that the oligonucleotides "collectively span at least 5 different array genes." The collective spanning could include only portions of the genes, and thus the independent claim does no include antecedent basis for the limitation.

In claim 21, the phrase "said at least 10 different array genes" lacks antecedent basis in claim 12. Claims 22-24 are indefinite because they depend from claim 21 and do not remedy this issue.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 2, 3, 4, 5, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modrich et al. (US 5459039) in view of Chee et al. (Science, Vol. 274, pages 610-614, 25 October 1996), and optionally, further in view of Brown *et al.* (US 5376526).

Modrich et al. teach a method for identifying mutations in a target DNA sequence which comprises

(a) hybridizing the target DNA with a control DNA sequence to create a duplex, wherein the control DNA sequence is the wild-type DNA corresponding to the target DNA sequence (Col. 7, lines 6-8), and wherein said target DNA comprises a pool of nucleotide segments that collectively span at least 10 different genes (Col. 10, lines 18-21);

(b) tagging any mismatch in said duplex with a detectable moiety, wherein the detectable moiety is a protein (Col. 7, lines 8-10);

(d) removing the segments tagged with the detectable moiety (Col. 16, lines 15-18), and

(f) identifying the gene and gene segment the selected mismatch belongs to (Col. 16, lines 45-50).

Modrich *et al.* teach a method for detecting genetic mutations. Modrich *et al.* teach that in the practice of this method the DNA molecules compared may comprise sequences encoding up to the entire genome of an organism, including man, and thus, such a sample necessarily comprises a pool of nucleotide segments that span at least 10 different genes.

Modrich *et al.* do not teach steps in which the duplex is cleaved into segments of 50-300 bases or in which the tagged segments are contacted with a mutation scanning array. Thus, the method taught by Modrich et al. differs from the claimed method only in that the methodology used to identify the gene and gene segment to which the selected mismatch belongs is different.

Chee *et al.* teach a mutation scanning array that comprises a plurality of elements, wherein the elements contain immobilized oligonucleotides 8-50 bases long, that collectively span at least 10 different genes from the 5'to 3' end, wherein the genes can be either coding regions or the genomic genes, to identify mutations in a target sequence. Chee *et al.* teach the identification of mutations within segments of the human mitochondrial genome via hybridization to an array for the entire mitochondiral genome (p. 612), thus simultaneously analyzing the control region, 12 protein coding regions, 22 tRNA genes, and 2 ribosomal RNA genes (p. 613), and suggest that future arrays should query the entire human genome, an estimated 100,000 genes (p. 613). Further, Chee *et al.* teach a step in which molecules were fragmented to an average size of less than 100 nucleotides prior to hybridization, and that fragmentation improved uniformity and specificity of hybridization (p. 613, note 12).

With regard to claim 2, this claim encompasses methods in which DNA is amplified prior to the hybridizing step of (a), as the claim requires that the segments are amplified prior to being used on the mutation scanning array. Thus, the claim encompasses a method in which the segments could be amplified and then tagged and be within the scope of this claim. Chee *et al.* teach methods which utilize amplified genomic extracts (note 11) and methods in which labels are added to sequences prior to hybridization via PCR amplification (note 12).

With respect to claims 3, 4, and 5, Chee *et al.* teach that the array contains a set of probes representing every position across the mitochondrial genome, in which whole genes are represented by elements containing immobilized oligonucleotides that sample in 25-300 bases for the whole mRNA sequence of the represented gene, and further non-coding portions of the genes (such as promoters) would be represented as the entire mitochondrial genome is represented.

With regard to claim 11, the array used by Chee *et al.* is a chip.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an array such as the one taught by Chee et al. for the identification of nucleic acid sequences containing mismatches identified by the method taught by Modrich *et al.* The ordinary practitioner would have been motivated by the teachings of Modrich et al. which provide that "any suitable analytical method (Col. 7, lines 40-42)" can be used to identify the fragments and by the teachings of Chee et al. who specifically provide nucleic acid arrays for the identification and localization of mutations in nucleic acid sequences. One would have been motivated to utilize the arrays taught by Chee *et al.* in order to take advantage of the benefits of microarray technology as taught by Chee *et al.*, for example, that

compared to conventional techniques such as sequencing, with the use of array technology "sequence reading at the level of data analysis is automated: The sequences can be read in a matter of minutes" and that the microarray technology is "highly scalable" (p. 612). Thus, in light of the teachings of Modrich et al. in view of Chee et al., the instant invention is prima facie obvious. Thus in the practice of such a method would necessarily have resulted in a step in which the segments identified using the screening methods taught by Modrich et al. (for example after the screening of an entire genome, as specifically taught by Modrich et al., or the mitochondrial genome, which is the exemplified subject of the studies of Chee et al.) are identified by contacting the segments to the array and identifying which array gene and gene segment thereof the mismatch belongs to.

Optionally, further motivation to combine the teachings provided by Modrich *et al.* in view of Chee *et al.* is provided by the teachings of Brown *et al.* Brown *et al.* teach a method for genomic mismatch scanning which identifies mismatches throughout a genome and then identifies the gene and gene segment which contain the mismatch (Col. 3, lines 5-10). The method taught by Brown *et al.* is very similar to that taught by Modrich *et al.*, in that large regions of DNA are screened for mismatches. Brown *et al.* specifically teach that the isolated DNAs of their invention preferably are hybridized with "a partial or complete collection of cloned, amplified, or synthentic DNA sequences corresponding to known genetic locations, immobilized in an ordered array on a solid substrate such as a membrane or a silicon or plastic chip (Col. 8, lines 18-23)." Chee *et al.* provide such an array. Thus, in view of the teachings set forth by Modrich *et al.* in view of Chee *et al.* and further in view of Brown *et al.*, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to

have utilized the mutation scanning array taught by Chee *et al.* for identification of the mismatched sequences taught by Modrich *et al.*

7. Claims 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modrich et al. in view of Chee et al., and optionally in view of Brown *et al.*, as applied to claims 1-5 and 11 above, and further in view of Cronin et al. (WO 98/30883).

The teachings of Modrich et al. in view of Chee et al., and optionally in view of Brown *et al.* are applied to the instant claim as they were to claims 1-4 and 11. Modrich et al. in view of Chee et al., and optionally in view of Brown *et al.* do not teach methods in which the genes on the array are selected because of their association with particular diseases.

Cronin et al. provide methods for the detection of polymorphisms and mutations in genes (ABSTRACT). The particularly teach that mutations can be searched for in reference sequences that include genes to many different types of diseases and conditions, including cancer, diabetes, and tumor suppressor genes (pages 12-13). Thus, it would have been prima facie obvious to one of ordinary skill in the art to have included any or all of these types of genes on an array to be used in a mutation detection method such as the one provided by Modrich et al. in view of Chee et al., and optionally in view of Brown *et al.* The ordinary practitioner would have been motivated to utilize arrays containing the coding and non-coding regions of disease genes in the methods taught by Modrich et al. in view of Chee et al., and optionally in view of Brown *et al.* in order to have used such arrays in further methods for the detection of disease associated mutations.

Response to Remarks

Claims 12 and 13 are allowed in view of the terminal disclaimer. Newly added claims 17, 19, 20, and 25 are allowed. Claims 16, 18, and 21-24 are rejected under 112 2nd paragraph but are free of the prior art. The closest prior art, as cited in this office action, does not teach steps of treating to remove spontaneous aldehydes, reacting with a repair glycosylase and then reacting with a compound of the formula X-Z-Y as recited in the instant claims.

Applicant states at page 11 of the remarks that previous technology to scan for polymorphisms and mutations was restricted to looking at mutations in a single specific gene, and does not teach or suggest how to detect unknown mutations in a population of many genes, further arguing that Modrich begins with a single known gene, rather than a population of multiple genes. This is not persuasive. Modrich *et al.* teach specifically teach that their method can be used to compare entire genomes, which certainly are comprised of hundreds of thousands of genes (Col. 10), and discuss in more detain the comparison of cloned fragments containing unknown sequence to the entire human genome (Col. 15, last paragraph). Thus, contrary to applicant's remarks, Modrich does teach screening a population of multiple genes.

Applicant argues in the paragraph bridging pages 11-12 that without a teaching to use the method of Modrich to screen multiple genes simultaneously, there is complete lack of motivation to combine the references except by impermissible hindsight. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was

made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case Modrich explicitly provides the element that applicant argues is absent.

Applicant continues the remarks with a discussion of the content of the Chee et al. reference and teaches that nothing in Chee suggests the mismatch detection methods of the present invention (p. 12). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The elements applicant argues are missing from Chee et al. are provided by Modrich and specifically addressed in the text of the rejection.

Applicant objects to the examiner's statement that the segments could be amplified and then tagged, submitting that the examiner uses impermissible hindsight reconstruction to provide motivation to combine isolated methods (see page 12 of the response). However, applicant is misconstruing the examiner's rejection. The sentence which is quoted by applicant is the examiner providing an interpretation of the claim which is clearly within the scope of the claim- the claim encompasses a method where fragments are first amplified and then tagged. Chee et al. exemplify a method in which genomic fragments are amplified prior to analysis for polymorphic positions. Thus, the combination of the methods of Modrich with those of Chee et al. would have resulted in a method that meets the limitations of claim 2. Applicant states that "similar arguments" are made in reference to claims 3, 4, 5, and 11. In each case, the examiner is pointing directly to how the limitations of the claims are taught in the references used to make

the rejection. The examiner never argues that the invention is not novel (as suggested in the final sentence of page 12); no rejection is made under 102. Instead the claims are rejected as being prima facie obvious, and the text of the rejection points to how each limitation of the claims is met by the references used to reject the claims.

At page 13 of the response, applicant states that Brown in no way cures the underlying defect in the combination of Modrich and Chee. This is not persuasive because the examiner is not persuaded by the arguments concerning the supposed defects in the combination of Modrich and Chee. Further with regardd to the rejections in further view of Cronin, applicant relies on the same arguments concerning the rejection in view of Modrich and Chee, optionally in view of Brown. These were not persuasive, as discussed herein. Thus, having carefully considered applicant's arguments, the rejections are MAINTAINED as applied to the amended claims.

Conclusion

8. Claims 12, 13, 17, 19, 20, and 25 are allowed.

9. Claims 16, 18, and 21-24 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Gifford *et al.* (US5750335) teach a method for mismatch detection wherein mismatches are tagged with a mismatch binding protein and subjected to subsequent PCR amplification prior to identification of the mismatch (see for example Figure 4).

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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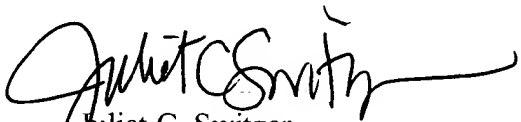

Juliet C. Switzer
Primary Examiner
Art Unit 1634

March 3, 2005